Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application.

The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Amendments to the claims were made for purposes of more clearly stating the claimed subject matter and do not add new matter or alter the scope of the claims.

Listing of Claims:

1.   (Currently amended) A method for constructing a gene network <u>of relationships</u> <u>between a plurality of genes of a set of genes and generating a graph representing the gene network</u> <u>of relationships between the genes</u> comprising the steps of:

(a)   providing a quantitative time course data library for <u>the</u> a set of genes of an organism, said library including expression results based on time course of expression of each gene in said set of genes, <u>wherein the expression results comprise gene expression data at a plurality of time points</u> <u>for each gene in said set of genes,</u> quantifying an average effect <u>on expression of each gene at each</u> <u>time point by each other of said genes at each time point,</u> and <u>quantifying</u> a measure of variability of <u>the effect on expression of each gene at</u> each time point on each other of said genes;

(b) creating a gene expression matrix from said library<u>, wherein the gene expression matrix</u> <u>comprises matrix data comprising the effects on expression of each gene at each time point by each</u> <u>other of said genes at each time point</u>;

(c) <u>applying a Bayesian computational model to the matrix data, wherein said Bayesian</u> <u>model comprises minimizing a BNRC$_{dynamic}$ criterion; and</u>

~~(e)~~ <u>(d)</u> generating <u>the gene</u> network <u>of</u> relationships between said genes <u>and generating a</u> <u>graph representing the gene network of relationships between said genes.</u>~~; and~~

~~(d) determining if one or more groups of genes is expressed differently from other of said~~ ~~groups of genes.~~

2.   (Cancelled)

3.   (Currently Amended) The method of claim 2̶1, wherein said step of minimizing a BNRC$_{dynamic}$ criterion comprises using a non-linear curve fitting method selected from the group consisting of polynomial bases, Fourier series, wavelet bases, regression spline bases and B-splines.

4.   (Currently amended) The method of claim 1, wherein said data library is created <u>by</u> <u>obtaining the gene expression data at the plurality of time points from a</u> u̶s̶i̶n̶g̶ time course study t̶o̶ a̶l̶t̶e̶r̶ g̶e̶n̶e̶ e̶x̶p̶r̶e̶s̶s̶i̶o̶n̶. <u>studying altering gene expression over time.</u>

5.   (Currently amended) The method of claim 2̶1, wherein said step of minimizing said BNRC$_{dynamic}$ criterion further comprises selecting a Bayesian mode using a backfitting algorithm.

6.   (Currently amended) The method of claim 2̶1, wherein said step of minimizing a BNRC$_{dynamic}$ criterion further comprises using Akaike's information criterion.

7.   (Currently amended) The method of claim 2̶1, wherein said step of minimizing a BNRC$_{dynamic}$ criterion further c̶o̶m̶p̶r̶i̶s̶i̶n̶g̶ <u>comprises</u> using maximum likelihood estimation.

8.   (Currently amended) The method of claim 1, wherein said <u>plurality of</u> genes are associated with a cell cycle <u>of the organism.</u>

9.   (Currently amended) The method of claim 2̶1, wherein said measure of variability is variance.

10.   (Currently amended) The method of claim 2̶1, wherein said non-linear curve fitting method is a non-parametric method.

11.   (Original) The method of claim 10, wherein said non-parametric method for minimizing a BNRC$_{dynamic}$ criterion includes using heterogeneous error variances.

12.   (Currently amended) The method of claim 11, wherein said step of minimizing a BNRC$_{dynamic}$ criterion further comprises the steps of:

(1) making a score matrix whose $(i, j)^{th}$ element is the $BNRC^j_{dynamic}$ score of the graph gene$_i \rightarrow$ gene$_j$;

(2) implementing one or more of ~~add, remove and reverse~~ adding the $BNRC^j_{dynamic}$ score of the effect of parent gene$_i$ on gene$_j$ to a calculation of $BNRC_{dynamic}$, removing the $BNRC^j_{dynamic}$ score of the effect of parent gene$_i$ on gene$_j$ to a calculation of $BNRC_{dynamic}$, and reversing the $BNRC^j_{dynamic}$ score of the effect of parent gene$_i$ on gene$_j$ to a calculation of $BNRC_{dynamic}$, which provides the smallest $BNRC_{dynamic}$; and

(3) repeating step 2 until the $BNRC_{dynamic}$ does not reduce further.

13. (Original) The method of claim 11, wherein said step of minimizing a $BNRC_{dynamic}$ criterion further comprises the step of applying a hill-climbing algorithm to minimize $BNRC^j_{dynamic}$.

14. (Currently amended) The method of claim 11, wherein an intensity of ~~the~~ an edge is determined using a bootstrap method.

15. (Currently amended) The method of claim 14, wherein said bootstrap method comprises the steps of:

(1) providing a bootstrap gene expression matrix by randomly sampling a number of times, with replacement, from the original gene library expression data;

(2) estimating the gene ~~genetic~~ network for gene$_i$ and gene$_j$;

(3) repeating steps (1) and (2) T times, thereby producing T gene ~~genetic~~ networks; and

(4) calculating the bootstrap edge intensity between gene$_i$ and gene$_j$ as $(t_1+t_2)/T$.

16. (Withdrawn) A method for elucidating a gene network, comprising the steps of:

(a) providing a raw data library of time-course gene expression data for a plurality of genes of an organism;

(b) subtracting background signal intensities from said raw data library;

(c)   calculating the relative change in gene expression for each of said plurality of genes;

(d)   analyzing the statistical significance of said relative in gene expression using Student's t-test; and

(e)   fitting said changes in gene expression to a linear spline function.

17.   (Withdrawn) The method of claim 16, further comprising the step of removing from consideration, those genes whose expression levels are sufficiently low so as to be determined predominantly by noise.

18.   (Currently amended) The method of claim 1, ~~wherein said step of grouping comprises~~ comprising grouping said genes into one or more equivalence sets.

19.   (Withdrawn) A method for estimating a gene network relationship, comprising the steps of:

(1)   Making a p x p matrix whose (i,j)th element is a BNRC score of the graph $gene_i \rightarrow gene_j$;

(2)   select a candidate set of parent $gene_i$ of $gene_j$ that gives a small BNRC score

(3)   select a computational order of said parent genes;

(4)   repeat the following steps;

    (4.1)   for genes either add a parent gene or delete a parent gene;

    (4.2)   recalculate $BNRC_{dynamic}$ score;

    (4.3)   repeat steps 3.1 and 3.2 until a suitable convergence criterion is satisfied;

(5)   permute the computational order of said parent genes in step (3);

(6)   repeat step (4); and

(7)   repeat steps (5) and (6) until $BNRC_{dynamic}$ is minimized.

20. (Currently Amended) A method for constructing a gene network model of a system containing a network of genes from time course gene expression data, said method ~~comprises~~ comprising:

applying ~~using~~ a Bayesian computational model to the time course gene expression data, wherein applying said Bayesian computational model comprises minimizing a BNRC$_{dynamic}$ criterion; and

generating a graph representing the gene network model resulting from applying the Bayesian computational model to the time course gene expression data wherein BNRC$_{dynamic}$ criterion is minimized.

21. (Original) The method of claim 20, wherein minimizing the BNRC$_{dynamic}$ criterion comprises using a non-linear curve fitting method selected from the group consisting of polynomial bases, Fourier series, wavelet bases, regression spline bases and B-splines.

22. (Currently amended) The method of claim 20, wherein minimizing the BNRC$_{dynamic}$ criterion comprises selecting a Bayesian ~~mode~~ model using a backfitting algorithm.

23. (Original) The method of claim 20, wherein minimizing the BNRC$_{dynamic}$ criterion comprises using Akaike's information criterion.

24. (Original) The method of claim 20, wherein minimizing the BNRC$_{dynamic}$ criterion comprises using maximum likelihood estimation.

25. (Original) The method of claim 20, wherein minimizing the BNRC$_{dynamic}$ criterion comprises using a non-linear curve fitting method, wherein the non-linear curve fitting method is a non-parametric method.

26. (Original) The method of claim 25, wherein the non-parametric method includes using heterogeneous error variances.

27. (Currently amended) The method of claim 26, wherein minimizing the BNRC$_{dynamic}$ criterion further comprises the steps of: (1) making a score matrix whose $(i, j)^{th}$ element is the

$BNRC_{dynamic}$ score of the graph $gene_i \rightarrow gene_j$; (2) implementing one or more of add, remove and reverse adding the $BNRC^j_{dynamic}$ score of the effect of parent $gene_i$ on $gene_j$ to a calculation of $BNRC_{dynamic}$, removing the $BNRC^j_{dynamic}$ score of the effect of parent $gene_i$ on $gene_j$ to a calculation of $BNRC_{dynamic}$, and reversing the $BNRC^j_{dynamic}$ score of the effect of parent $gene_i$ on $gene_j$ to a calculation of $BNRC_{dynamic}$, which provides the smallest $BNRC_{dynamic}$; and (3) repeating step 2 until the $BNRC_{dynamic}$ does not reduce further.

28.   (Currently amended) The method of claim 26, wherein minimizing the $BNRC_{dynamic}$ criterion further comprises the step of applying a hill-climbing algorithm to minimize the $BNRC^{(j)}_{dynamic}$.

29.   (Currently amended) The method of claim 26, wherein an intensity of the an edge is determined using a bootstrap method.

30.   (Currently amended) The method of claim 29, wherein said bootstrap method comprises the steps of:

(1)   providing a bootstrap gene expression matrix by randomly sampling a number of times, with replacement, from the original gene library expression data;

(2)   estimating the gene genetic network for $gene_i$ and $gene_j$;

(3)   repeating steps (1) and (2) T times, thereby producing T gene genetic networks; and

(4)   calculating the bootstrap edge intensity between $gene_i$ and $gene_j$ as $(t_1 + t_2)/T$.

31.   (Cancelled)

32.   (Cancelled)

33.   (Cancelled)

34.   (Cancelled)

35.　(Withdrawn)　A method for identifying a target gene in a system containing a gene network, comprising: (a) constructing a first and second gene network model using a Bayesian computational model, wherein said Bayesian computational model comprises minimizing a $BNRC_{dynamic}$ criterion, wherein the first gene network model is obtained by analyzing a first gene expression profile and the second gene network model is obtained by analyzing a second gene expression profile, and wherein the first gene expression profile is obtained from the system at a first time point and the second gene expression profile is obtained from the system at a second time point after said first time point, and (b) analyzing the first and second gene network model using said Bayesian computational model, wherein the time course of gene expression is quantified, and wherein a parent gene is identified as the target gene.

36.　(Withdrawn)　The method of claim 35, wherein the target gene is a parent gene.

37.　(Withdrawn)　The method of claim 35, wherein the target gene is a gene downstream from a parent gene.

38.　(Withdrawn)　A data file containing the identity of one or more target genes obtained according to the method of claim 35.

39.　(Withdrawn)　The data file of claim 38 in a computer readable form.

40.　(Withdrawn)　The data file of claim 38 accessible from a remote location.

41.　(Withdrawn)　The data file of claim 38 accessible from an internet web location.

42.　(Withdrawn)　A method of providing a service comprising (1) receiving a data set from a party, said data set comprising time course expression data of a group of genes; and (2) determining network relationships between genes in said group by minimizing a $BNRC_{dynamic}$ criterion.

43.　(Withdrawn)　The method of claim 42, wherein receiving said data set comprises receiving the identity of at least one of said genes.

44.   (Withdrawn) A method of providing a service comprising receiving an agent from a party, and identifying a target gene for the party using the gene network model constructed according to the method of claim 35.